An Enzymatic Chromatin Switch that Directs Formation of Active Brown Fat

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How is the recruitment of brown adipocytes regulated? Ohno et al. (2013) show that the euchromatic histone-lysine N-metyltransferase 1 (EHMT1) is essential for the specification of the brown adipocyte fate, a finding with important implications for the pathophysiology of obesity and obesity-related maladies.

We have been blessed with several types of adipose tissue, enabling adaptation to cold weather and to fluctuations in the availability of food. Whereas white adipose tissue (WAT), with its richness in energy-dense triglycerides, functions as a buffer against fluctuations in energy availability, brown adipose tissue (BAT) has the capacity to uncouple mitochondrial respiration and produce heat. Recent work identified a third type of fat cell—called beige or brite—with properties distinct from either white or brown adipocytes (Wu et al., 2012). The mechanisms that determine each of these fates are still unclear. Work from Ohno et al. (2013) examining the generation of brown adipocytes from *Myf5*$^+$ precursors now identifies an enzymatic chromatin switch, regulated by the histone methyltransferase euchromatic histone-lysine N-metyltransferase 1 (EHMT1), as a key factor in the development of brown adipocytes.

More than 30 years ago, Taylor and Jones (1979) demonstrated that when a cell line of mesodermal origin (3T310T1/2) was treated with 5-azacytidine, a cytidine analog, the cells differentiated into myocytes or adipocytes. Thus, prevention of methylation on cytidine residues by incorporation of this nucleotide analog into the cell's DNA leads to activation of cellular differentiation programs that result in the formation of myocytes and adipocytes. Apart from demonstrating the importance of epigenetic events, these findings also suggested a close interrelationship between myocytes and adipocytes. We have since learned that "classical" brown adipocytes (and myocytes) arise from *Myf5*$^+$ precursor cells and form the thermogenic interscapular brown fat depot (Seale et al., 2008) that is essential for the survival of small mammals, including infants, in cold environments (Lidell et al., 2013). This process is mediated by the formation of a PRDM16-C/EBPβ transcriptional complex that activates and maintains the brown adipocyte gene program and, conversely, suppresses myogenesis (Kajimura et al., 2009). Beige adipocytes arise from *Myf5*$^-$ precursor cell populations and are found interspersed within WAT. Based on cell-autonomous differences between classical brown, beige, and white adipocytes, Wu et al. (2012) recently confirmed that these cells constitute three distinct types of adipocytes.

Exactly how the switch from *Myf5*$^+$ precursors to brown adipocytes operates is an open question that has recently been addressed by Ohno et al. (2013). The authors studied the mechanism by which the PRDM16-C/EBPβ complex acts to induce PPARγ expression, a prerequisite for brown fat development (Kajimura et al., 2009). Using deletion mutants of PRDM16, Ohno et al. (2013) demonstrate that the EHMT1 is the only methyltransferase that copurifies with PRDM16 complexes that are capable of supporting brown adipocyte differentiation. Ohno et al. (2013) then show that EHMT1 is the main methyltransferase of the PRDM16 complex in brown adipocytes and that EHMT1 and PRDM16 act synergistically to enhance PPARγ transcriptional activity. *Ehmt1*^{myf5} knockout mice, lacking EHMT1 in cells derived from *Myf5*$^+$ precursors, such as classical brown adipocytes, have less developed interscapular brown fat, smaller brown adipocytes, and a gene expression profile with a broad reduction of BAT-related genes, findings that collectively support a fundamental role for EHMT1 in the specification of classical brown adipocytes versus muscle. By modulating EHMT1 levels in C2C12 myoblasts, Ohno et al. (2013) show that EHMT1 activity is crucial for the inhibitory effect of PRDM16 on the myogenic gene program. EHMT1 promotes BAT formation by inducing the epigenetic marks H3K9me2 and H3K9me3 at promoter regions of genes that positively regulate a myogenic gene program, thereby repressing muscle formation. This action prepares the precursor cells for entering the brown adipocyte differentiation program. Furthermore, Ohno et al. (2013) convincingly demonstrate that EHMT1 positively regulates the thermogenic gene program. Finally, mice lacking EHMT1 in cells expressing an adiponectin-cre construct (*Ehmt1*^{adipo} knockout mice), i.e., in brown and white adipocytes, have reduced adaptive thermogenesis and display several features of dysfunctional metabolism, such as reduced glucose tolerance and increased levels of liver triglycerides. Thus, EHMT1 appears to be important not only for the formation of BAT, but also for its biological function.

Perhaps the most interesting feature of EHTM1 is that it provides a distinct enzymatic activity that, from a physiological standpoint, has the ability to regulate the delicate balance between muscle and BAT formation. What are the physiological regulators of EHTM1 activity? Will chronic exposure to cold result in increased EHTM1 activity, thereby promoting formation of BAT? Ohno et al. (2013) provide a clue when they show that a β3-adrenergic receptor agonist (CL316,243), which mimics the physiological response to

cold, is less effective in inducing the formation of beige adipocytes in the inguinal WAT depot of *Ehmt1*^{adipo} knockout mice than in wild-type mice. Since Ohno et al. (2013) mainly studied the effect of EHMT1 on classical brown adipocytes derived from *Myf5*$^{+}$ precursors, it is an open question as to whether the molecular machinery underlying this effect in beige adipocytes is similar to that in classical brown adipocytes. Another question relates to the bipotential precursor cells described by Lee et al. (2012), which can develop into either white or brown adipocytes depending on the type of stimulation: activation of β3-adrenergic receptor leads to the formation of brown adipocytes, while a high-fat diet stimulates the differentiation of white adipocytes. Are such cells derived from a population of precursors that avoided a muscle destiny by appropriately regulating EHTM1? One more exciting issue is how the early B cell factor 2 (Ebf2) relates to EHTM1. Ebf2 also regulates PPARγ activity and acts as a key transcriptional regulator of brown fat cell fate and function (Rajakumari et al., 2013). This factor may act synergistically with EHTM1 since it recruits PPARγ to BAT-selective target genes (Rajakumari et al., 2013), an action that appears to be complementary to the inhibition of muscle gene expression mediated by EHMT1.

The recent findings deciphering the transcriptional and chromatin code that regulates brown fat formation and function are important not only from a biological science perspective. They also provide new pathways and molecules that can be tested and targeted for therapeutic purposes so that the beneficial effects of having ample amounts of brown fat can be harnessed and made available to the many who suffer from obesity and obesity-related maladies, such as type 2 diabetes.

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Synaptic Plasticity and the Warburg Effect

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Functional brain imaging studies show that in certain brain regions glucose utilization exceeds oxygen consumption, indicating the predominance of aerobic glycolysis. In this issue, Goyal et al. (2014) report that this metabolic profile is associated with an enrichment in the expression of genes involved in synaptic plasticity and remodeling processes.

Aerobic glycolysis (AG), also known as the Warburg effect, is a metabolic hallmark of cancer cells (Warburg, 1956). It consists of production of lactate from glucose in the presence of oxygen. As it turns out, some brain areas and cell types can also process glucose in this way. Studies at the whole organ level have shown already decades ago (for Review, see Allaman and Magistretti, 2013) that glucose utilization by the brain is in excess of oxygen consumption by about 10%, implying a nonoxidative use of glucose entering the brain. Functional brain imaging studies have identified in the adult brain areas such as the dorsolateral prefrontal cortex, superior and medial frontal gyrus, precuneus and posterior cingulate cortex, in which AG predominates, accounting for 25% of glucose utilization, whereas in other areas such as the cerebellum AG is virtually nonexistent (Vaishnavi et al., 2010). As far as cell types are concerned, astrocytes (glial cells) are the major sites of AG in the brain (Bélanger et al., 2011).

The question then arises of the function of AG in these specific locales. In an